Medical and Pediatric Oncology 30:175–177 (1998)

Role of Staging Bone Marrow Examination in Children With Hodgkin Disease

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Purpose. To determine the value of bone marrow trephine biopsy as part of the clinical staging for children presenting with Hodgkin disease.

Patients and Methods. A retrospective study of pre-treatment bone marrow examinations was undertaken to examine the value of bone marrow staging in children with Hodgkin disease. The records of 122 children, diagnosed with Hodgkin disease at Texas Children's Hospital between February 1960 and July 1996, were reviewed. Age, sex, complete blood counts (CBC), pathology, and clinical and pathological staging results were tabulated.

Results. Information was complete for analysis in 110 patients. Bone marrow trephine biopsies identified Hodgkin disease in 2/110 patients (1.8%). The patients with bone marrow disease had clinical stage IIIB disease prebiopsy. Positive bone marrow biopsy results did not effect a change in therapy, and the small number of positive cases do not allow any prediction as to prognosis.

Conclusion. There is no role for bone marrow trephine examination in children with clinical stage I-IIIA Hodgkin disease. Med. Pediatr. Oncol. 30:175–177, 1998.

Key words: bone marrow trephine biopsy; Hodgkin disease; staging

During the last three decades, the diagnosis and management of Hodgkin disease in children has changed significantly, resulting in a dramatic improvement in overall survival. Recent studies show a 10-year overall survival of 91% for children with localized disease and a 3-year event-free survival (EFS) of 87% with advanced stage disease [1,2]. Advanced imaging technologies, leading to more accurate clinical staging, and the use of effective combination chemotherapy and/or involved field radiation therapy have produced these results.

Bone marrow trephine biopsy examinations have been an essential part of the clinical staging of patients with Hodgkin disease [3–5]. The incidence of bone marrow infiltration in adult patients at diagnosis is estimated at between 2 and 32% [6–12]. Few reports discuss bone marrow involvement in pediatric cases of Hodgkin disease [2,13–15]. Therefore, we initiated a review of pediatric cases of Hodgkin disease at our center to determine the incidence of bone marrow invasion at diagnosis and to estimate the prognostic impact of bone marrow involvement for survival.

PATIENTS AND METHODS

Patient Eligibility

The records of all children, less than 19 years of age, with Hodgkin disease, evaluated at Texas Children's Hospital, between February 1960 and July 1996, were reviewed. Data reviewed included: physical examination, complete blood count (CBC), serum copper, sedimentation rate (ESR), alkaline phosphatase, lactic dehydrogenase (LDH), and chest radiographs. Diagnostic imaging techniques for staging of Hodgkin disease at this institution have evolved over the 36-year period of this review. Prior to 1982, all patients underwent lymphangiography. From 1976, Gallium scans were used. From 1982, lymphangiography was replaced by computed tomographic scans of the chest and the abdomen/pelvis. Staging laparotomy was performed in the usual fashion [4].

Twelve patients were excluded from analysis: 2 did not undergo bone marrow examinations, 3 patients did not complete clinical or pathological staging procedures, 6 patients were for second opinions only, and 1 patient was incorrectly diagnosed. One hundred and ten (110) cases of Hodgkin disease were finally identified and form the basis of this report.

Histopathology

Patients were staged according to the Ann Arbor classification [3]. Histologic confirmation of Hodgkin disease was performed in the Texas Children's Hospital Department of Pathology, with subclassification according to Lukes-Butler [16]. Bone marrow aspirates and Jamshidi

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biopsies (unilateral or bilateral) were obtained from posterior superior iliac crests. The bone marrow trephine biopsies were fixed and decalcified in Zenker solution and stained with hematoxylin and eosin. When indicated, reticulum stain was used to determine the degree of fibrosis [17]. The diagnostic criteria for bone marrow invasion was based on published descriptions from the Ann Arbor Conference [18,19]. Findings include typical Reed-Sternberg cells or their mononuclear variants within a suitable cellular background, usually including areas of fibrosis. All bone marrow materials were reviewed by two investigators and positive marrows were defined according to the above criteria.

RESULTS

There were 110 patients less than 19 years of age with Hodgkin disease included in the analysis. The median age at diagnosis was 11.9 years (range 2.5–18.2 years). Five patients were younger than four years at diagnosis. There were 78 males and 32 females (ratio 2.4:1). Ethnic characteristics included: Caucasian 64%, Hispanic 23%, Black 11%, other 2%. Thirty-three patients were clinically staged and 77 patients were pathologically staged. The histologic classification of the 110 cases reviewed include: Lymphocyte predominent—13 (12%), nodular sclerosing—59 (53%), mixed cellularity—33 (30%), lymphocyte depleted—2 (2%), not classified—3 (3%). The final staging of the 110 cases was: Stage I, 22 (20%); Stage II, 41 (37%); Stage III, 35 (32%); and Stage IV, 12 (11%).

A total of 139 bone marrow biopsies from 110 patients were reviewed (bilateral examinations—29 patients; unilateral—81). Two patients (1.8%) had bone marrow involvement at diagnosis. Patient 1 was an 8-year old Hispanic male who presented with persistent fever, weight loss, extensive adenopathy above and below the diaphragm, anemia and a node biopsy consistent with Hodgkin disease, lymphocyte depleted. Bone marrow aspirates were cellular and biopsy revealed large atypical mononuclear cells scattered within a stroma of histiocytes, plasma cells, eosinophils, and fibrosis. He achieved complete remission with combination chemotherapy but relapsed 38 months from diagnosis. Following salvage chemotherapy, he has remained in second remission for 12+ years. Patient 2 was a 12-year-old Black male who presented with persistent fever, weight loss, diffuse adenopathy above and below the diaphragm, anemia, and node biopsy consistent with Hodgkin disease, mixed cellularity. Bone marrow aspirates were hypocellular and biopsy revealed areas of fibrosis with histiocytes and Reed-Sternberg cells. The patient achieved remission with combination chemotherapy, relapsed 24 months from diagnosis, and ultimately expired with refractory disease.

In contrast, 108 patients (98.2%) had no evidence of Hodgkin disease on bone marrow examination. Among 79 patients with initial clinical stage I-IVA, no evidence of bone marrow invasion was detected. Among patients with B-symptoms at presentation, marrow invasion was detected in only 6% (2/31). Among all with stage III/IV disease, marrow invasion was present in only 4% (2/47). There was no significant difference between CBC, ESR, alkaline phosphatase, LDH, or serum copper for patients with or without marrow involvement (data not shown). Both patients with bone marrow invasion experienced nodal relapses and 1 expired. In comparison, 7/10 patients otherwise pathologically staged as IV without bone marrow invasion are alive in continuous remission.

DISCUSSION

There are no published series on the incidence of bone marrow invasion with Hodgkin disease in a pediatric case population. In contrast, a survey of the literature revealed the average incidence of bone marrow involvement in adult patients to be 13–14%, with a range of 2–32% [6]. Characteristics associated with an increased incidence of bone marrow involvement from these series include male gender, older age, cytopenias, and either mixed cellularity or lymphocyte depletion [6–9,11,12]. Advanced stage disease and the presence of B-symptoms have also been associated with an increased incidence of marrow invasion ranging from 25–45% [6,7,12]. There are no comparable published series in pediatric Hodgkin disease that address the incidence of marrow invasion and associations with cytopenias, histologic subtypes, or clinical staging.

In our retrospective review of 110 children with untreated Hodgkin disease, the overall incidence of bone marrow invasion was 1.8%. Although 75% of our patients had only unilateral biopsies, Bartl et al. observed that a large single biopsy was as effective as two smaller biopsies for detecting marrow involvement.[6] In our pediatric series, no clinical correlations were established for affected cases. Children with advanced stage disease and/or B-symptoms had a 4–8% incidence of marrow invasion. In the absence of B-symptomatology, no child had evidence of marrow invasion. Though both of our patients with marrow invasion at diagnosis relapsed, these cases are too few to make long-term prognostic projections.

Bone marrow trephine biopsies are unpleasant procedures for children and add expense to an otherwise costly staging procedure. Bone marrow biopsies continue to be recommended in the staging of pediatric patients with low stage Hodgkin disease [20]. Based on our review,

bone marrow trephine biopsies do not appear warranted in patients under 19 years of age with clinical stage I–IIIA disease. Further study is necessary to determine whether bone marrow infiltration has prognostic significance in children with B symptomatology and advanced stage Hodgkin disease.

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